'Immunomodulatory' approaches to the management of antiphospholipid syndrome

"*The use of immunomodulatory agents has revolutionized the management of many autoimmune diseases including rheumatoid arthritis and SLE. Despite the comparatively slow pace of implementing these therapeutic agents in the management of APS patients, the last few years have produced several excellent clinical studies highlighting the efficacy of these drugs as well as international collaborative initiatives dedicated to furthering APS research.*"

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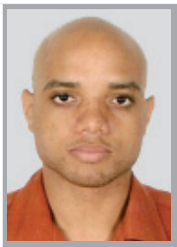

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"He who would learn to fly one day must first learn to stand and walk and run and climb and dance; one cannot fly into flying."

This quote by Friedrich Nietzsche describes quite aptly the burgeoning role of immunomodulatory therapy in treating patients with antiphospholipid syndrome (APS).

Despite the syndrome being first characterized almost 30 years ago, the approach to management of these patients has remained relatively unchanged. It is widely accepted that the treatment and prevention of thrombosis, a clinical hallmark of the syndrome, in APS patients is based on conventional anticoagulation therapy with heparin, low-dose aspirin or warfarin singly or in combination depending on the clinical scenario [1]. However, some patients are refractory to therapy, still experiencing thrombosis despite compliance while many patients experience bleeding as a complication. Warfarin therapy can also be quite onerous since frequent blood monitoring and dietary and lifestyle alterations are required, and it is also unsuitable for treating pregnant patients. Additionally, the management of patients persistently positive for antiphospholipid antibodies (aPL) remains a controversial issue, some physicians recommending low-dose aspirin despite there being no evidence-based data demonstrating that alone it is sufficient for primary thromboprophylaxis [2].

So, can 'immunomodulatory' drugs provide a viable alternative to conventional anticoagulation therapy in APS? A precept for the utilization of these drugs in treating any autoimmune disease is an understanding of the disease's pathophysiology, in particular the abnormally activated immune pathways and signaling molecules. There is extensive evidence to suggest that pathogenic aPL, rather than causing thrombosis directly, induces a procoagulant phenotype by activating endothelial cells (ECs), monocytes, platelets and coagulation factors that facilitates a 'secondary event' such as infection or trauma which then induces thrombosis [3]. Immunomodulation is an attractive approach to the management of APS since there is data from *in vitro* and *in vivo* animal studies highlighting several putative molecular targets but perhaps more importantly, these targets represent an 'early' phase in the pathology of the disease. Theoretically, blocking the 'early' activity of pathogenic aPL on target cells could result in less harmful and more efficacious therapy, reducing the risk for thrombosis in the event of an inciting 'secondary' event.

So why has there been a delay in implementation? Although there is evidence demonstrating the pathogenic effects of aPL, controversy still exists concerning the standardization of antibody detection as well as the strength of the association of these antibodies with the development of thrombosis and pregnancy morbidity. More importantly, the mechanisms of aPL inducing these pathogenic effects are incompletely understood. Perhaps the most significant roadblock however is the inability to mount adequate clinical research initiatives due to insufficient funding and poorly defined patient cohorts to study the disease prospectively. The fact that the major clinical event in the disease, thrombosis, is relatively rare makes it necessary to enroll a large number of patients to adequately power any trial. These problems were addressed in earnest at the

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13th International Congress on Antiphospholipid Antibodies held in Galveston, TX, USA in April 2010 by a Clinical Research Task Force. The work of this task force gave birth to what is now the largest international alliance dedicated to APS research, Antiphospholipid Syndrome: Alliance for Clinical Trials and International Networking (APS ACTION). The first objective of this alliance is to mount a clinical trial to investigate the efficacy of hydroxychloroquine (HCQ) therapy in preventing primary thrombosis in persistently aPL-positive primary APS patients without a history of thrombosis. Additionally, there is recently published clinical data suggesting a beneficial effect of statin therapy and rituximab therapy in treating APS. Other immunomodulatory drugs may also prove useful including inhibitors of tissue factor (TF), complement, p38MAPK, NF-κB and aPL binding to their target cells. In this regard, it is possible that APS may have different pathogenetic mechanisms in different patients, in that the propensity for thrombosis may be explained in some by complement activation for example, and in others by other mechanisms, such as the ones mentioned above involving TF, antibody binding or intracellular signaling, either working alone or in concert. In the future, it may be possible to develop a more precise phenotypic profile in distinct APS patient subpopulations in an effort to more precisely identify and target the specific mechanism(s) involved.

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HCQ therapy

HCQ initially found its clinical usefulness as an antimalarial drug but since then has proven to possess a myriad of anti-inflammatory and immunomodulatory effects including modulation of endosomal function, antigen processing and T- and B-cell signaling [4]. Interestingly, HCQ also has antithrombotic properties through its effect on inhibiting platelet activation and aggregation and has been used historically as a prophylactic agent against deep vein thrombosis and pulmonary embolism after hip replacement surgeries [5]. Nowadays, HCQ is considered an essential part of the management of systemic lupus erythematosus (SLE) patients with proven clinical efficacy in decreasing risk of flares and damage accrual as well as protecting against vascular events including arterial thrombosis [6]. However, with regards to the potential utilization of HCQ therapy in treating APS patients, clinical data are still lacking. *In vitro* and *in vivo* studies have demonstrated the ability of HCQ to limit aPL-induced thrombus formation and platelet GPIIb/IIIa receptor expression in a dose-dependent manner and to reverse binding of aPL-β2GPI complexes to phospholipid bilayers [7]. HCQ was shown to be somewhat protective against a primary thrombotic event in asymptomatic aPL-positive patients using logistic regression analysis in a cross-sectional study [8]. There is still however insufficient data to recommend HCQ for primary or secondary thrombosis prevention but it might be an appropriate adjunctive therapeutic agent in APS patients who develop recurrent thrombosis despite optimum anticoagulation. The upcoming clinical trial being performed under the auspices of APS ACTION will ideally provide meaningful clinical data outlining the usefulness of HCQ in preventing thrombosis in APS and cultivate guidelines regarding its use in these patients.

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Statin therapy

Both *in vitro* studies utilizing ECs and murine studies have demonstrated the beneficial effects of fluvastatin in abrogating the thrombogenic and proinflammatory effects of aPL antibodies, independent of the drug's cholesterol lowering effects [9]. This protective effect was also demonstrated for another statin, rosuvastatin, utilizing human umbilical vein ECs exposed to serum from an APS patient in an *in vitro* model [10]. Interestingly, by employing a proteomic analytical approach, Cuadrado *et al.* were able to show that aPL-induced inflammatory proteins can be reversed following a month-long course of fluvastatin therapy [11]. Quite recently, Murthy *et al.* presented preliminary data from an ongoing pilot study [101] examining the effect of fluvastatin therapy in persistently aPL-positive patients with or without SLE. The data show that a 3-month course of 40-mg fluvastatin significantly reduced the proinflammatory and prothrombotic biomarkers IL-6, IL-1b, soluble (s)TF, sICAM-1, sVCAM-1 and E-selectin [12].

No conclusive evidence exists however for a beneficial effect of statins in reducing thrombosis risk in APS patients, but it is conceivable that in reducing the upregulation of prothrombotic/proinflammatory cytokines in ECs and monocytes, a reduction in thrombosis risk would be the result. The use of statin therapy is especially attractive for persistently aPL-positive patients without a history of thrombosis. Further mechanistic and clinical studies need to be done to delineate the role that statin therapy will play in treating APS patients.

Rituximab therapy

A systematic review of published data regarding the use of rituximab therapy in APS revealed several case reports of successful treatment in primary, secondary and catastrophic APS patients and in patients with aPL and autoimmune-mediated thrombocytopenia and hemolytic anemia [13]. Erkan *et al.*, who are conducting an open-label Phase II clinical trial using rituximab to treat aPL-positive patients resistant to conventional anticoagulation (RITAPS) [102] reported at the 2011 American College of Rheumatology meeting that despite a lack of an overall decrease in aPL titers, rituximab therapy resulted in decreased CD19+ B cells with an improvement in thrombocytopenia and resolution of skin ulceration [14].

Other immunomodulatory drugs

Specific inhibition of TF with agents such as dilazep and inhibition of NF-κB and p38MAPK are potentially very promising therapeutic approaches in APS management. TF plays a central role in aPL-induced thrombosis and the activation of ECs, monocytes and platelets by aPL results in signaling mainly through the p38MAPK pathway and NF-κB activation. Specific inhibition of these targets has been shown to reduce aPL-induced TF upregulation in monocytes and ECs and aPL-enhanced thrombosis in mice [15,16].

Peptides that mimic domains I and V of β2GPI inhibit specific binding of aPL to β2GPI and β2GPI to target cells, respectively, and the peptide TIFI, a structural analogue of the phospholipid binding region of domain V, decreases thrombus size in aPL-injected mice [17].

Similarly, inhibition of cell-surface receptors including apolipoprotein E receptor 2′, Toll-like receptor 4 and annexin A2 result in abrogation of aPL-mediated pathogenic effects in *in vitro* and *in vivo* animal models [18].

Complement inhibitors, particularly C3 and C5 inhibitors, have also been demonstrated to ameliorate aPL-induced thrombosis and pregnancy complications using *in vitro* and *in vivo* murine models [19,20]. Clinical trials are necessary to delineate the potential role these agents will play in treating the disease.

Conclusion

The use of immunomodulatory agents has revolutionized the management of many autoimmune diseases including rheumatoid arthritis and SLE. Despite the comparatively slow pace of implementing these therapeutic agents in the management of APS patients, the last few years have produced several excellent clinical studies highlighting the efficacy of these drugs as well as international collaborative initiatives dedicated to furthering APS research. This will ideally translate the very promising preclinical data we have into meaningful therapeutic guidelines for managing APS patients. We have been slowly "learning to stand and walk and run and climb" but through the sustained efforts of these global research initiatives, the hope is that the safe and effective treatment with immunodulatory drugs in APS patients 'will take flight' in the near future.

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